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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)	
28385/35415	

Application Number	Filed
09/529,053-Conf. #1413	April 6, 2000

First Named Inventor: James W. Waldman et al.

Art Unit	Examiner
1617	S. Wang

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant /inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 33,547

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. _____

Li-Hsien Rin-Laures
Signature

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Typed or printed name

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Telephone number

February 16, 2007
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV 532468442 US, on the date shown below in an envelope addressed to:
MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Dated: February 16, 2007 Signature: _____ (Juan Quintero)

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Currently pending independent claim 34:

34. A method of treating a patient suffering from a viral infection comprising administering to said patient (a) a therapeutically effective amount of a leflunomide product and (b) a pyrimidine compound without antiviral activity. (See amendment mailed August 23, 2006.)

Previous claim 34 prior to amendment:

34. A method of treating a patient suffering from a viral infection comprising administering to said patient a therapeutically effective amount of a leflunomide product and administering to said patient a pyrimidine compound in an amount effective to enhance serum levels of uridine, cytidine or thymidine. (See amendment mailed February 27, 2006.)

Background

The present invention is directed towards treating viral infection with leflunomide product and with a pyrimidine compound that increases levels of the naturally occurring nucleotides uridine, cytidine or thymidine. Applicants discovered that leflunomide product has anti-viral activity against a variety of viruses, and that the toxicity of leflunomide product can be reversed by additionally administering pyrimidine compounds that increase levels of uridine, cytidine or thymidine.

Leflunomide product has at least two effects: inhibition of protein tyrosine kinase activity, and inhibition of dihydroorotate dehydrogenase, a key enzyme in the biosynthesis of pyrimidine nucleotide triphosphates. See page 1, lines 17-20 of the background in the specification. The latter activity, inhibition of pyrimidine nucleotide synthesis, leads to reduced pyrimidine nucleotide levels and causes toxicity. However, one of ordinary skill in the art would have believed that both of these effects of leflunomide product were likely necessary for its anti-viral activity and would not have been motivated to interfere with either effect.

It was Applicants' discovery that the inhibition of pyrimidine nucleotide synthesis was not necessary for anti-viral activity. Thus, Applicants' disclosure that increasing serum uridine, cytidine or thymidine levels can reverse toxicity (by restoring the cell and patient to normal pyrimidine levels) without interfering with the anti-viral activity of leflunomide product is surprising and nonobvious.

A. Currently pending claim 34 is allowable

In the Office Action mailed November 16, 2006, currently pending claim 34 was deemed free of the art. The only outstanding rejection is that the phrase "pyrimidine compound without antiviral activity" lacks written descriptive support and is new matter.

The Examiner erred in ignoring Applicants' factual evidence that one of ordinary skill in the art would understand from reading the specification that Applicants were in possession of the claimed invention. See Declaration of Walter Atwood, Ph.D. (filed December 21, 2006). Applicants submitted this declaratory evidence promptly after the first time that the new matter rejection was made.

For the reasons briefly stated below and explained in the Declaration and accompanying Transmittal (filed December 21, 2006), the written description/new matter rejection should be withdrawn.

a. Dr. Atwood's declaration provides evidence that the definition of pyrimidine compound in the specification excludes pyrimidine compounds with anti-viral activity.

b. Dr. Atwood's declaration provides evidence that one of ordinary skill in the art would have understood that the inventors were claiming the administration of pyrimidine compounds without antiviral activity.

c. Portions of Dr. Atwood's declaration are excerpted below:

> The definition of pyrimidine compound confirms that the contemplated pyrimidine compounds ***would not have*** anti-***viral activity***. A pyrimidine compound is defined at page 20, lines 12-14 of the application as 'compounds useful either directly or as intermediates in pathways for supplying pyrimidine nucleotides (uridine, cytidine and thymidine).' [Para. 8]
>
> It is clear, from reading the application, that the pyrimidine compounds to be co-administered with leflunomide product were not intended to have antiviral activity. I base my conclusion on the facts that (a) the stated purpose of the pyrimidine compound was to reduce toxicity of the leflunomide product, not for an anti-viral effect, and (b) the definition of pyrimidine compound excludes pyrimidine compounds with anti-viral activity. [Para. 10]
>
> Therefore, one of ordinary skill in the art as of March 11, 1998, upon reading the application, would have understood that the inventors were claiming the administration of pyrimidine compounds ***without antiviral activity***. [Para. 11]

B. Prior claim 34 (in the amendment mailed February 27, 2006) is allowable

1. The Examiner erred in an arbitrary and capricious manner by refusing to enter Applicants' amendment filed December 7, 2006. Applicants requested return of claim 34 to its prior wording of February 27, 2006, which had already been considered and examined.

2. The sole rejection of prior claim 34 was under 35 U.S.C. 103(a) as assertedly obvious over Weithmann et al., U.S. Pat. No. 5,556,870, and Hammer, AIDS 1996, vol. 10, suppl 3, s1-s11. (See office action mailed May 23, 2006.) The Examiner committed legal error because the cited references do not disclose all elements of prior claim 34, and therefore a *prima facie* case of obviousness cannot be made, and because the Examiner ignored Applicants' unexpected results, which would rebut any *prima facie* case.

Hammer, the only reference cited as disclosing pyrimidine compounds, does not disclose all claim limitations because it does not disclose pyrimidine compounds that "enhance serum levels of uridine, cytidine or thymidine" as recited in prior claim 34. Hammer discloses anti-HIV nucleoside analogs, which do not enhance serum levels of uridine, cytidine or thymidine. Applicants supplied references and reasoning to support their position. See pages 6-8 of Applicants' response filed December 7, 2006, and briefly summarized below. Thus, the obviousness rejection should be withdrawn because of (1) failure to disclose all claim limitations and (2) unexpected results.

a. The Examiner erred by ignoring Applicants' evidence and scientific reasoning that the anti-HIV nucleoside analogs disclosed in Hammer do not enhance serum levels of uridine, cytidine or thymidine (the naturally occurring nucleosides that form the building blocks of DNA and RNA, see paragraph 8 of the Atwood Declaration). The nucleoside analogs discussed in Hammer exert their anti-viral effect precisely because they are non-natural analogs. Anti-viral nucleoside analogs inhibit the activity of reverse transcriptase, thereby inhibiting viral DNA synthesis. Thus, the basis for their anti-retroviral activity is their ability to act unlike natural nucleosides.

b. The Examiner failed to show how Hammer discloses, suggests or motivates one to administer a pyrimidine that does "enhance serum levels of uridine, cytidine or thymidine" to treat viral infection, as recited in prior claim 34. Hammer would teach away from administering compounds that supply naturally occurring nucleosides, because it is the non-natural analogs that are taught to have the anti-viral activity.

c. The Examiner erred by ignoring Applicants' evidence and scientific reasoning that administering the anti-HIV nucleoside analogs of Hammer would not provide the unexpected beneficial effects of the claimed combination (reduction in leflunomide toxicity). The reduction in toxicity occurs because the supply of naturally occurring nucleosides is increased, an effect that Hammer does not teach. In fact, the nucleoside analogs of Hammer themselves cause toxic effects resulting from their interference with normal DNA synthesis. [See Exhibits B and C to Applicants' response filed February 27, 2006]. Compounds that would further interfere with pyrimidine kinetics, either synthesis or utilization, would be expected to increase leflunomide product toxicity, and would therefore not be useful in the claimed treatment methods.

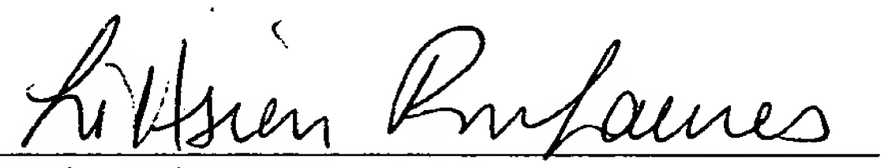
Conclusion

For all of the reasons, Applicants respectfully submit that the Examiner has erred and that the panel should allow currently pending claim 34 (and all claims dependent thereon), or suggest allowance of prior claim 34 (and all claims dependent thereon).

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

February 16, 2007



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